REMARKS

Claims 66-69 and 71-78 are pending in this Application.

ISSUES UNDER 35 U.S.C. § 103

Claims 66-69 and 71-78 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Siegel in view of Feinstein U.S. Patent 4,572,203 (Feinstein) and Cerny et al. U.S. Patent 4,957,656 (Cerny) and Schutt U.S. Patent 5,605,673 (Schutt). Examiner notes that Siegel teaches the use of saline solution as a carrier of his Echogen, and that employing a Dextrose 5% solution would have been well within the level of ordinary skill in the art, because such solutions are art equivalent substitutes. The Examiner states that using D5W as a carrier and perfluorocarbon as a suitable gas would have been well within the general knowledge available to one of ordinary skill in the art. The Examiner states that Schutt provides a reasonable degree of expectation of success for the ordinary artisan to use perfluorobutane or perfluoropropane and enhance coronary flow with a thrombolytic agent. Examiner states that the combined teachings of the references meet all elements of the instant claims, but also provide reasonable expectation of success to satisfy an obviousness rejection. Examiner further states that "Applicant has not provided any evidence of unexpected results rebutting the rejection."

Applicants respectfully traverse this rejection.

Applicant continues to assert that that Examiner has not established a prima facie case of obviousness. The Examiner has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). In order for the Examiner to establish a *prima facie* case of obviousness, three base criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to

combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *M.P.E.P.* § 2142 (citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed.Cir. 1991)).

The present invention relates to a method of relieving trauma associated with obstruction of vessels distal to a thrombus site by increasing blood flow with or without thrombus dissolution and recanalization in animals comprising:

introducing a pharmaceutical composition to an animal with a thrombus by intravenous injection, said pharmaceutical composition comprising a microbubble ultrasound agent, and a pharmaceutically acceptable carrier, wherein said carrier comprises a 5% solution of dextrose and thereafter;

applying ultrasound to the area of trauma distal to the thrombus site.

To render the invention obvious, the combination of the cited art must teach or suggest the claimed invention. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed.Cir. 1991). While Siegel discloses a method for "reducing and removing a thrombosis disposed within a body vessel by radiating an ultrasound imaging agent ... proximate the thrombosis vessel," (Col 2), there is no teaching or suggestion of a method for relieving trauma associated with obstruction of vessels distal to a thrombus site by increasing blood flow with or without thrombus dissolution and recanalization in animals. Siegel teaches nothing about recanalization or the benefits of ultrasound without thrombus dissolution. In fact Siegel specifically directs that ultrasound be directed to the thrombus to dissolve it, column 5, lines 8-14.

In contrast Applicant applies ultrasound distal to the thrombus site as stated in claim 1.

Furthermore, while Schutt discloses the use perfluorobutane or perfluoropropane in microbubbles, Schutt does not teach or suggest that the bubbles themselves will enhance coronary flow or be useful in treating trauma associated with obstruction of vessels distal to a thrombus site. Similarly, neither Feinstein nor Cerny, which incorporates the teachings of Feinstein, teach or suggest that microbubbles themselves may be used to enhance coronary flow for treating trauma associated with obstruction of vessels distal to a thrombus site. Both teach the use of microbubbles for imaging, not for increasing blood flow. In particular, Feinstein states that the "microparticles may be used for imaging a wide variety of areas" (Col 7) and that the "microparticles may be useful in delineating changes in myocardial tissue perfusion due to interventions such as ... use of thrombolytic agents (such as streptokinase) to dissolve clots." (Col 8, emphasis supplied).

Therefore, the references either alone or when combined do not teach or suggest all the claim elements.

Claim 66 is therefore not rendered obvious by Siegel et al. in view of Feinstein U.S. Patent 4,572,203 (Feinstein) and Cerny et al. U.S. Patent 5,957,656 (Cerny) and Schutt U.S. Patent 5,605,673 (Schutt). Claim 67 is likewise nonobvious as dependent on claim 66 that is nonobvious as claim 67 contains all of the limitations of claim 66.

Claims 68-69, 72 and 75 are dependent on claim 67. Since the claim 67 method is nonobvious, claims 68-69, 72 and 75 which are dependent on claim 67 and focus on this method are likewise nonobvious.

Claim 71 is dependent on claim 68. Claim 71 is the method of claim 68 wherein the protein coated microbubbles are albumin coated microspheres. Since the method of claim 68 is

nonobvious based on the nonobvious method claim from 67, claim 71 which includes protein coated microbubbles are albumin coated microspheres is likewise nonobvious.

Claims 73 and 74 are dependent on nononbvious claim 72. The method of claim 72 is the method of claim 67 wherein the insoluble gas is selected from the group consisting perfluoromethane, perfluoroethane, perfluoropropane, perfluorobutane, and perfluoropentane. Since the method of claim 72 is nonobvious based on the nonobvious claim 67, the methods dependent on claim 72 wherein said perfluorocarbon gas is perfluorobutane (claim 73) and wherein said perfluorocarbon gas is perfluoropropane (claim 74) are both likewise nonobvious.

Claims 76-78 recite a method dependent on the method of claim 75. Claim 75 depends on the method of claim 67 further comprising the following steps: mixing an aqueous solution comprising 2% to about 10% by weight of human serum albumin diluted about 2-fold to about 8-fold with 5% to 50% by weight dextrose; and exposing said solution to a sonication horn to generate stable microbubbles from about .1 to 10 microns in diameter to create said pharmaceutical composition. The method of claim 75 is nonobvious in view of the nonobvious claim 67 method, and, therefore, claims 76-78 are nonobvious.

Therefore, Applicant respectfully requests withdrawal of the claims rejected under 35 U.S.C. § 103(a). Reconsideration is respectfully requested.

This is a request under the provision of 37 CFR § 1.136(a) to extend the period for filing a response in the above-identified application for one month from August 21, 2003 to September 21, 2003. Applicant is a small entity; therefore, please charge Deposit Account number 26-0084 in the amount of $55.00 for one month to cover the cost of the extension. Any deficiency or overpayment should be charged or credited to Deposit Account 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,

Heidi S. Nebel, Reg. No. 37,719
McKEE, VOORHEES & SEASE, P.L.C.
801 Grand Avenue, Suite 3200
Des Moines, Iowa 50309-2721
Phone No: (515) 288-3667
Fax No: (515) 288-1338
CUSTOMER NO: 27140

Attorneys of Record

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